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VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS

PhRMA

April 6, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on Clinical Lactation Studies-Study Design, Data Analysis, and Recommendations for Labeling [Docket 2005D-0030, 70 *Federal Register*, 6697 (February 8, 2005)

Dear Madam/Sir:

The following comments on the subject draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA members invested an estimated $38.8 billion in 2004 in discovering and developing new medicines. PhRMA companies are leading the way in the search for new cures.

We appreciate the opportunity to provide the attached comments on the draft guidance on clinical lactation studies and thank you in advance for your consideration of these comments as you finalized the guidance. Please contact me if you have any questions.

Sincerely,

Alice E. Till

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CC Kathleen Uhl (CDER)
Toni Stifano (CBER)

2005D-0030 C 4

Comments on Draft FDA Guidance: Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling

General

There is a clear public health benefit to understanding the disposition of drugs in lactating women and their breast-fed infants. There has been little formal assessment of drug entry into breast milk, as is pointed out in the draft guidance. It is important to provide clear and accurate information on the potential impact of drug exposure on lactation and we agree that "consistent application of adequate study designs" yielding such data would be of benefit to lactating women and their health care providers. [Lines 131-133].

While it is clear that certain drugs are excreted in breast milk, there is no consistent evidence that this additional route of clearance has led to therapeutic failure in the mother, and evidence of toxicity in neonates and young children due to drug exposure in breast milk are limited to case reports. The safety of neonates and young children is, of course, paramount. And in the interest of safety, invasive testing should only be done when necessary.

At issue, though not clearly stated in this document, is how to determine when drug clearance into breast milk might be a significant clinical issue, and thus require pharmacokinetic assessment. Also, it is not clear from this guidance whether there is an expectation that lactation studies would be required for approval, or might be optional. We suggest that the principal aim of clinical lactation studies should be to address any potential effects of lactation on the PK/PD of the women taking the drug, the effects of the drug on milk production and composition and the potential risk of drug transfer via breast milk. Studies to address these objectives are not the most appropriate designs to assess potential impact on the infant and should be used as triggers for more work only in those cases where it is clear that a significant exposure would occur. The level of drug exposure in milk that would trigger pharmacokinetic studies in the breast fed child should be defined. As noted in the guidance [lines 74-76] presence of a drug in the breast milk does not necessarily indicate a health risk for the breast fed child.

The range and extent of assessments suggested appear to be elaborate, given the absence of clearly defined clinical risks. In some cases, the assessments are impractical (e.g. trying to get the time course of drug concentrations and/or drug pharmacodynamics in a baby of <6months), or validation of unique assays (e.g. in tears; lines 408-410). Children are most at risk of drug effects in the early postnatal period; most drug metabolizing enzymes mature rapidly after birth. Therefore, serial assessment of pharmacokinetics in infants in longitudinal studies should not be recommended.

We suggest that the draft guidance provide a stepwise approach to the conduct of clinical lactation studies: e.g. for compounds with characteristics where assessment **might** be appropriate, to perform simultaneous plasma and milk assessment in the mother only

(IV.B.1); in cases where **appreciable** drug excretion in breast milk is demonstrated, to potentially assess exposure in the breast fed child. The difficulty and complexity of simultaneous PK assessment of mother-infant pairs realistically makes this an unlikely option and we suggest that this should not be listed as the first assessment example.

Comments and Recommendations

Line 32. Introduction, fourth bullet.
We suggest deletion of this bullet. If determination of the effects of exposure for a particular drug in breast-fed infants is needed, then more targeted studies in the infant should be designed. This should not be a trigger for a clinical lactation study.

Lines 88 – 115. Maternal Pharmacokinetics.
There is little evidence that lactation affects or is likely to affect maternal pharmacokinetics for most drugs. If lactation affects the maternal pharmacokinetics it is likely that the clinical importance is limited. Any analysis of maternal pharmacokinetic data should be descriptive only, similar to the evaluation of pharmacokinetics in other special populations such as persons with renal failure, rather than using formal pharmacokinetic equivalence guidelines.

Lines 139 – 169. Considerations for When to Conduct a Clinical Lactation Study.
We are concerned regarding the broad applicability of this Guidance to products under development as well as those that are currently marketed. The bulleted list on Page 4 (Lines 136-151) appears to capture all medications that can be used by women in their reproductive years rather than focusing on those products for which there is a greater potential for harm to infants who are breast-feeding. Greater guidance should be provided as to when it is important to conduct clinical lactation studies and when it is not necessary to conduct these studies based on scientific information or based on experience and exposure. For example, biotechnology-derived products typically have none to negligible oral bioavailability and are not usually excreted in breast milk. Hence, the likelihood of a breast-fed infant exhibiting systemic exposure is exceedingly low and a study seems unnecessary. The potentially problematic drugs are lipophilic weak bases, polychlorinated biphenyls or polybrominated biphenyls, or compounds that undergo active transport into milk. This perspective should be provided as part of the guidance. We suggest that Page 4 emphasize that sponsors should evaluate products for which the consequences of uninformed dosing of mothers are suspected to be important to the health of infants who are breast-feeding.

In addition, the Guidance would benefit from a more specific discussion of the timing of lactation studies within the continuum of drug development and marketing.

Lines 142, 147, and 150.
The term "women of childbearing potential" might be more appropriate than the term "women of reproductive age" as there are examples of drugs that have reproductive

toxicology issues, where their use is restricted in women of childbearing potential but not in sterilized women of reproductive age (e.g. atorvastatin).

Lines 171 – 174. Animal Models.
Since lacteal transfer is principally governed by the physicochemical properties of a drug molecule, evaluation in preclinical species may well be helpful in understanding the potential for lacteal excretion and could provide guidance to a sponsor regarding whether or not a human study is needed. For example, the materno-fetal guinea pig model has been established in academia for the study of drug transfer into breast milk. The Guidance should discuss in greater detail appropriate animal models. On line 173, our recommendation is to delete the clause beginning with, "but these models do not help…"

Lines 195 – 198. Study Design Considerations.
If a drug exhibits linear pharmacokinetics, including drugs that accumulate and are given chronically, single dose studies should be sufficient to predict effects which would be observed at steady-state.

Lines 204 – 229. Mother-Infant Pair Design.
This option should not be considered first line testing but should be considered only after studies done in lactating women alone and only if significant presence of the drug in breast milk raises concern for significant exposure to the breast-fed infant.

Line 213.
It may be difficult to quantify the effects of drugs on milk production given small sample sizes, and the possible confounding influence of external non-pharmacological factors. In general there is a clear pharmacological rationale for those drugs shown to affect milk production (estrogens, dopamine agonists and antagonists).

Lines 218 – 220.
Pharmacokinetics in infants are better performed in a pediatric program rather than as part of a lactation study. This type of study design will only provide information on "oral clearance" for the parent drug and exposure information for parent and metabolite. It will not provide information on the fraction of drug absorbed nor on total clearance of drug or metabolite. It is recommended that the wording in this paragraph be clarified.

Lines 268 – 287. Lactating Women (Milk Only).
The rationale for "milk only" studies is unclear. Obtaining pharmacokinetic data in milk in the absence of corresponding pharmacokinetic data makes it difficult to achieve the objectives stated in this section.

Lines 289 – 352. Other Design Considerations.
For most drugs, assessments of drug levels in milk at various times in the lactation process is not necessary, as the amount of drug in milk does not provide a significant dose to the child under any conditions. Therefore, the longitudinal and multiple arm studies should rarely, if ever, be considered.

Lines 341 – 352. Controls.
The document should describe what potential physiologic processes would affect drug disposition in the mother. If one is concerned about major differences in pharmacokinetics, these can be assessed using historical controls. It is not necessary to assess pharmacokinetics in the mother after weaning is complete, nor is the use of control, non-lactating volunteers likely to yield much useful information.

Lines 377 – 414. Sample Collection and Analysis.
Milk samples at a certain collection time, i.e. x hours after dosing, could be combined from both breasts. However, collection intervals analogous to urine collection intervals (e.g. the 4-8 hours dosing used in the guidance example) and pooling of samples collected at different times should never be used. Milk is stored in highly vascular alveoli, where there is ample opportunity for bi-directional movement of drug between milk and plasma. This is the entire basis for the calculation of the M/P ratio. Thus milk concentrations represent an instantaneous or nearly instantaneous reflection of drug content, not the time averaged excretion of drug represented by a sample of urine that has been collecting in the bladder over a number of hours.

Greater discussion should be provided on when to consider the collection of colostrum or milk fractions such as foremilk and hindmilk.

Lines 495 - 500. Table.
The table on page 12 should reflect the appropriate analysis, focusing on AUC in milk over an interval rather than the collection interval analysis